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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/911,088	07/23/2001	David W. Ow	16313-0052	4013

29052 7590 05/07/2003

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EXAMINER
HELMER, GEORGIA L

ART UNIT	PAPER NUMBER
1638	14

DATE MAILED: 05/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/911,088	OW, DAVID W.	
	Examiner	Art Unit	
	Georgia L. Helmer	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-66* is/are pending in the application.

4a) Of the above claim(s) *17-34 and 37-66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,35 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Restriction election

1. The Office acknowledges the receipt of Applicant's restriction election, Paper No. 13, filed 7 March 2003. Applicant elects Group X, directed to Claims 1-16, 35 and 36, directed to methods of obtaining site-specific gene replacement as the related to ϕC31 integrase, Cre reversible recombinases and plant cells, with traverse. Applicant traverses, stating primarily that Examiner has not demonstrated that it would be a serious burden to search and examine all of the claims together; that the two groups of claims are within the same class and subclass, and therefore easily search together. Applicant's traversal has been considered and is unpersuasive because even though the search of the two groups of claims may overlap, they are not coextensive, and therefore would constitute a search burden. Further more, the fact that the class and subclass of the two groups of claims are the same is not a determining factor. Applicant traverses, stating primarily that the two inventions are not independent or distinct as claimed, and that Groups X and Y are dependent since the two groups claims a method of using two or more irreversible recombinase sites in the same construct to achieve site-specific gene replacement, and further than the two groups are not distinct in nature since Group X would not be patentable over Group Y. Applicant's traversal has been considered and is unpersuasive because the Group Y claims use different and additional steps, as well as additional starting materials, to produce a different products that than of Group X. Furthermore, Claim 1 link(s) inventions *X* and *Y*, and the restriction requirement between the linked inventions is subject to the nonallowance of

the linking claim(s), claim 1. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application.

2. Claims 1-66 are pending. Claims 1-16, 35 and 36 are examined in this action. Claims 17-34 and 37-66 are withdrawn as being drawn to non-elected inventions. This restriction is made FINAL.

Information Disclosure Statement

3. Initialed and dated copies of Applicant's IDS form 1449, Papers No. 5 and 12, filed 1 October 2001 and 19 February 2003, respectively, are attached to the instant Office action.

Claim Rejections - 35 USC § 112-second

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

5. Claims 1-16, 35 and 36 are rejected under 35 U.S.C. 112-2nd.

In claim 1, and all claims dependent thereon,

- "gene" is unclear because a "gene" implies a DNA sequence that exists in nature and includes coding and noncoding regions, as well as all regulatory sequences associated with expression. Since this does not appear to be Applicant's intention, the language "a DNA of interest" is suggested. Or Applicant may recite the various components of the "gene". All subsequent recitations of this language are also rejected.

In (a), "receptor polynucleotide" is unclear because it is not apparent how a "receptor polynucleotide" differs from a polynucleotide.

- Also, "two or more of" is unclear because what "two or more of" refers to is unclear—does this mean copies?
- It is unclear whether the recitations within the parentheticals, for example, (IRS) and (CIRS), are limitations in the claim, or have some other meaning.

In (b), "donor polynucleotide" is unclear because it is not apparent how a "donor polynucleotide" differs from a polynucleotide.

- Also, "two or more of" is unclear because what "two or more of" refers to is unclear—does this mean copies, for example?

In (d), "the first and second types of recombination sites" lacks antecedent basis.

- Also, polynucleotide recombination occurs between nucleic acids, not between "types" of polynucleotides.

Claim 12 is drawn to a "negative selectable marker". What does this mean?

Clarification/correction is required.

Claim Rejections - 35 USC § 112-Enablement

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-16, 35 and 36 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of obtaining site-specific gene replacement in an *Arabidopsis thaliana* cell (as described in Example 8, pages 49-54 and Table 3, p. 54) comprising (a) providing a Arabidopsis thaliana plant comprising a cell comprising the chromosomal DNA segment: *loxP-35S-PP'-npt-35S-int-PP'-inverted loxP*, where PP' is the attP site of the ϕC31 recombination system, npt is the coding region of neomycin transferase, and int encodes the ϕC31 recombination system integrase, (as described on pg 50, specification, ¶165),(b) introducing by sexual crossing, the chromosomal DNA segment: BB'-bar-loxP-P3-gus-(inverted loxP)-35S-BB'-dhlA-35S-accC1, where bar encodes resistance of basta, P3 is a sugarcane bacilliform badnavirus promoter, gus is the coding regions of β-glucuronidase, dhlA is the coding region for haloalkane dehalogenase, and aacC1 encodes resistance to gentamycin, (as described in ¶166, page 50), and (c) where the ϕC31 integrase catalyzes recombination between the PP' and the BB' recombination sites, to form a

replacement, does not reasonably provide enablement for all eukaryotic cells, all plant cells, all methods of introducing, and all irreversible recombinases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to methods of obtaining site-specific gene replacement in a eukaryotic cell comprising providing a eukaryotic cell that comprises a receptor construct wherein the receptor construct comprises a receptor polynucleotide flanked by two or more of a irreversible recombinase site, introducing into the cell a donor construct that comprises a donor polynucleotide flanked by two or more of a irreversible complementary recombinase site, and contacting the receptor construct and the donor construct with an irreversible recombinase site polypeptide, wherein the irreversible recombinase site catalyzes recombination between the first and second types of recombination sites and replacement of the receptor polynucleotide with the donor polynucleotide, thereby forming a replacement construct; wherein the donor construct is linear, circular or a chromosome, wherein the receptor construct is a chromosome, where the receptor construct comprises two irreversible recombinase site and the donor construct comprises two irreversible complementary recombinase sites, where irreversible recombinase sites are inverted with respect to each other and the irreversible complementary recombinase site are inverted with respect to each other, where the donor polynucleotide further comprises a promoter and a gene of interest, where the receptor construct comprises a promoter adjacent to one of the irreversible

recombinase site, where the promoter is 5' to the irreversible recombinase site, where the receptor construct comprising a second promoter operably linked to a selectable marker, where the receptor construct or the donor construct includes a negative selectable marker , where the receptor polynucleotide or the donor polynucleotide comprises a nucleic acid encoding the irreversible recombinase polypeptide, where the irreversible recombinase polypeptide is a bacteriophage ϕC31 integrase, where the eukaryotic cell is a mammalian cell or a plant cell.

The enablement issues include: *all plants*.

Enablement is considered in view of the *Wands* factors (MPEP 2164.01(a

The breadth of the claims and the nature of the invention. The claims are drawn to methods of obtaining site-specific gene replacement in a eukaryotic cell comprising providing a eukaryotic cell that comprises a receptor construct wherein the receptor construct comprises a receptor polynucleotide flanked by two or more of a irreversible recombinase site, introducing into the cell a donor construct that comprises a donor polynucleotide flanked by two or more of a irreversible complementary recombinase site, and contacting the receptor construct and the donor construct with an irreversible recombinase site polypeptide, wherein the irreversible recombinase site catalyzes recombination between the first and second types of recombination sites and replacement of the receptor polynucleotide with the donor polynucleotide, thereby forming a replacement construct; wherein the donor construct is linear, circular or a

chromosome, wherein the receptor construct is a chromosome, where the receptor construct comprises two irreversible recombinase site and the donor construct comprises two irreversible complementary recombinase sites, where irreversible recombinase sites are inverted with respect to each other and the irreversible complementary recombinase site are inverted with respect to each other, where the donor polynucleotide further comprises a promoter and a gene of interest, where the receptor construct comprises a promoter adjacent to one of the irreversible recombinase site, where the promoter is 5' to the irreversible recombinase site, where the receptor construct comprising a second promoter operably linked to a selectable marker, where the receptor construct or the donor construct includes a negative selectable marker, where the receptor polynucleotide or the donor polynucleotide comprises a nucleic acid encoding the irreversible recombinase polypeptide, where the irreversible recombinase polypeptide is a bacteriophage ϕC31 integrase, where the eukaryotic cell is a mammalian cell or a plant cell.

The state of the art and the predictability or lack thereof:

Re all plants: Applicant claims all plant cells. Applicant teaches Arabidopsis thaliana plant cells and plants. Arabidopsis thaliana is not representative of all plants. Rather Arabidopsis thaliana is special in that Arabidopsis thaliana has the smallest known plant genome size--(7x10exp7 bp), see (Buchanan, et al. Biochemistry & Molecular Biology of Plants (2000) American Society of Plant Physiologists, Rockville Md 20855, p. 322, last paragraph). Plant genomes vary in size from that of Arabidopsis thaliana to larger

than 10exp11 (Figure 7.19, p323). Arabidopsis thaliana is an excellent model system for plant genetics because of its small genome size and because of Arabidopsis thaliana's lifestyle, short generation time, small plant size, and other well know advantages. Molecular manipulations of plants having larger genome sizes, are more difficult to manipulate because of the sheer physical quantity of DNA. It is unpredictable that all plants would be equally amenable to chromosomal replacement manipulation as is Arabidopsis thaliana. Applicant has provided no guidance on how to predictably eliminate inoperable embodiments from a virtually ad infinitum of possibilities other than by random trial and error, which is excessive experimentation and an undue burden.

In view of the breadth of the claims (any eukaryotic cell, any plant cell, and any irreversible recombinase), the unpredictability of the art, undue trial and error experimentations would be required to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

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Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

9. Claims 1-11, 13-16 and 35 are rejected under 35 U.S.C. 102(a) as being anticipated by Groth, et. al., A Phage integrase directs efficient site-specific integration in human cells, Proc. Natl. Acad. Sci. USA, vol. 97, no. 11, May 23, 2000, pages 5995-6000, Applicant's IDS.

Groth et. al. teaches a methods of obtaining site-specific gene replacement in a eukaryotic cell (p. 5996, 2nd column) comprising providing a eukaryotic cell that comprises a receptor construct wherein the receptor construct comprises a receptor polynucleotide flanked by two or more of a irreversible recombinase sites, introducing into the cell a donor construct that comprises a donor polynucleotide flanked by two or more of a irreversible complementary recombinase site, and contacting the receptor construct and the donor construct with an irreversible recombinase site polypeptide, wherein the irreversible recombinase site catalyzes recombination between the first and second types of recombination sites and replacement of the receptor polynucleotide with the donor polynucleotide, thereby forming a replacement construct; where the cell is a mammalian cell (p. 5996, 2nd column), where the receptor construct is linear or circular vector (Figure 1, p 5996), a chromosome (p 5999, column 1, last ¶), where the donor construct is a chromosome (p 5999, column 1, last ¶), and where the irreversible recombinase is bacteriophage ϕC31 integrase (Abstract and p. 5995, column 2).

Accordingly, Groth anticipates the claimed invention.

Remarks

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Georgia L. Helmer whose telephone number is 703-308-7023. The examiner can normally be reached on 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 703-306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Customer Service, whose telephone number is 703-308-0196.

Georgia Helmer PhD
Patent Examiner
Art Group 1638
May 5, 2003

ELIZABETH F. McELWAIN
PRIMARY EXAMINER
GROUP 1600